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Impacts of early intervention with fluoxetine following early neonatal immune activation on depression-like behaviors and body weight in mice

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ABSTRACT

Several reports have suggested that early neonatal immune activation adversely influences the hypothalamic–pituitary–adrenal (HPA) axis development in humans and animal models. In addition, there have been several studies indicating that early intervention with fluoxetine (FLX) can alter HPA axis development and function, and prevent occurrence of behavioral abnormalities induced by common early-life insults. The present study aims to investigate the effects of early intervention with FLX following early neonatal immune activation on depression-like behaviors and body weight in mice. Neonatal mice in their postnatal days (PNDs) 3 and 5 received either lipopolysaccharide (LPS; 50 μg/kg, s.c.) or saline treatment, then male and female mice of both neonatal intervention groups received oral administration of FLX (5 and 10 mg/kg/day) or water via regular drinking bottles during the periadolescent period (PNDs 35–65). The results showed that neonatal LPS exposure elevated depression-like behaviors accompanied by increasing corticosterone levels in adulthood and decreasing body weight during neonatal and adolescent periods. Furthermore, the periadolescent FLX treatment inhibited the depression-like behaviors induced by neonatal infection in both sexes. This study obtained some experimental evidence indicating the potential adverse impacts of the FLX on normal behavioral development in male control animals. In conclusion, our findings suggest that an early pharmacological intervention with FLX may prevent emergence of depression-like behaviors induced by neonatal immune challenge without any detrimental effect on health in a sex- and dose-dependent manner in mice.

1. Introduction

There is a great deal of evidence from human and animal studies indicating that adverse events in neonatal period can negatively affect the trajectory of normal brain development and function of physiological and behavioral systems across the life span (Korosi et al., 2011; Lee and Dammann, 2011; Pesonen and Räikkönen, 2011; Skripuletz et al., 2010; Walker et al., 2011; Zakharova, 2009). Several experimental models have proven a significant link between neonatal exposure to inflammatory agents like lipopolysaccharide (LPS) and increased likelihood of neuropsychiatric disorders in later life. In this context, multilaboratory studies have shown that LPS-induced neonatal immune activation alters hypothalamic–pituitary–adrenal (HPA) axis activity (Nilsson et al., 2002; Shanks et al., 1995, 2000) resulting in modifications of physiological (Iwasa et al., 2010), immunological (Boissé et al., 2004), behavioral (Shanks et al., 1995), and neuroendocrine (Iwasa et al., 2009) systems in adulthood.

Previous studies have indicated that LPS exposure on postnatal days (PNDs) 3 and 5 facilitates anxiety-like behaviors in adult rats (Sominsky et al., 2011; Walker et al., 2004, 2009). However, little attention has so far been devoted to the evaluation of early postnatal inflammation impacts on depression-like behaviors in animal models. In this regard, we and others have shown that there might be an association between anxiety and depression-like behaviors (Beuke et al., 2003; Enayati et al., 2012) in which genes likely have a crucial role as well as the etiology of these two behaviors (Field et al., 2010; Kendler et al., 2007; Williamson et al., 2005). Although,

Abbreviations: LPS, lipopolysaccharide; HPA, hypothalamic–pituitary–adrenal; PND, postnatal day; FLX, fluoxetine; SSRI, selective serotonin reuptake inhibitor; COR, corticosterone; FST, forced swimming test; TST, tail suspension test; ANOVA, analysis of variance; NPY, neuropeptide Y; IL, interleukin; TNF-α, tumor necrosis factor-alpha; BDNF, brain derived neurotrophic factor.

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